

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/HR2005/000008

International filing date (day/month/year)
27.01.2005

Priority date (day/month/year)
30.01.2004

International Patent Classification (IPC) or both national classification and IPC
A61K31/38, A61K31/381, A61K31/55, A61P29/00

Applicant
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1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/HR2005/000008

IP20 Rec'd PCT/PTO 28 JUL 2006

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/HR2005/000008

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-15
	No: Claims	
Inventive step (IS)	Yes: Claims	1-15
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-15
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/HR2005/000008

Re Item V

**Reasoned statement with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

1. The present application according to **claim 1** relates to the use of benzonaphthoazulene compounds of the specified general formula I for the manufacture of pharmaceutical formulations for the treatment and prevention of diseases, damages and disorders of the central nervous system caused by disorders of neurochemical equilibrium of biogenic amines or other neurotransmitters.
2. Reference is made to the following documents:
D1: WO 03/084961 A (PLIVA D.D; MERCEP, MLADEN; MESIC, MILAN; PESIC, DIJANA; OZIMEC, IVANA;) 16 October 2003;
D2: US 2003/153750 A1 (MERCEP MLADEN ET AL) 14 August 2003;
D3: SPERLING W ET AL: "New tetracyclic antidepressants" DRUGS OF TODAY 1997 SPAIN, vol. 33, no. 2, 1997, pages 95-102, XP002100053 ISSN: 0025-7656;
D4: WO 99/19317 A (JANSSEN PHARMACEUTICA N.V; ANDRES-GIL, JOSE IGNACIO; FERNANDEZ-GADEA,) 22 April 1999.

If not indicated otherwise, the relevant passages are those mentioned in the International Search Report.

3. The present application meets the requirements of the PCT with respect to novelty (Art. 33(2)).

D1 and **D2** disclose the same benzonaphthoazulene compounds of the present application as TNF-alpha inhibitors and as analgetic agents.

D3 and **D4** disclose tetracyclic compounds sharing some degree of structural similarity with the present compounds useful for the treatment of a number of CNS disorders and conditions.

Thus, none of the prior art documents is novelty destroying for the present application.

4. The present application also satisfies the requirements of the PCT with respect to inventive step (Art. 33(3)).

D1, which is regarded as the closest prior art, discloses the compounds of the present application as analgetic agents. The present application differs from **D1** in that the compounds are therapeutically useful in connection with the treatment of various CNS conditions.

Thus, the *problem* to be solved by the present application is the finding of other therapeutic uses for the benzonaphthoazulene compounds disclosed in **D1**. The *solution* provided by the present application is not rendered obvious by any prior art document, either alone or in combination.

5. For the assessment of the present claims 1-15 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment (such as present claims 1-15).

Re Item VIII

Certain observations on the international application

6. Present claims 1-9 and 11-15 do not meet the requirements of Art. 6 PCT because the pathologies are not clearly defined. Independent claim 1 (and also dependent claim 11) refer to the cause of the CNS diseases, damages or diseases but do not address the specific pathologies. However, the specific pathologies are clearly defined in present claim 10..